

Research Communication

A Di-Aza-Benzo Crown Ether Derived from *p*-*tert*-Butyl Calix[4]arene. Synthesis and Complexation of Zinc Cation

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Abstract. Di-aza-benzo crown ether *p*-*tert*-butyl calix[4]arene (**1**) has been prepared by hydrogenating the already known Schiff-base precursor (**2**). The metal ion complexing ability of (**1**) toward zinc cation is presented. The formation of a 2 : 1 (Zn : (**1**)) complex and the location of zinc cations were deduced from ¹H-NMR investigations.

Key words: 1,3-Bridged *p*-*tert*-butyl calix[4]arene, complexation of zinc cation.

1. Introduction

Calixarenes are a relatively new family of macrocyclic compounds whose conformational and chemical versatility has attracted organic chemists dealing with host-guest chemistry [1, 2]. In this family, calix[4]arenes can be readily functionalized at the upper and/or lower rim [1, 2]. Functionalizations at the lower rim associated with enforced conformations led to the design and synthesis of ligands preorganized for metal complexation. For example, the 1,3-selective capping of *p*-*tert*-butyl calix[4]arene with suitable metal coordinating bridges gave rise to macrobicyclic receptors such as calixcrowns [3], calixspherands [4], calixcryptands [5], calix(aza-)crowns [6, 7], and Schiff-base calix[4]arenes [8]. These macrocyclic receptors were mainly used for the coordination of alkali and alkaline earth metals except for calix(aza-)crowns [6] which showed interactions with softer di- and trivalent cations and Schiff-base calix[4]arenes [8] which complexed lanthanides, heavy and transition metals.

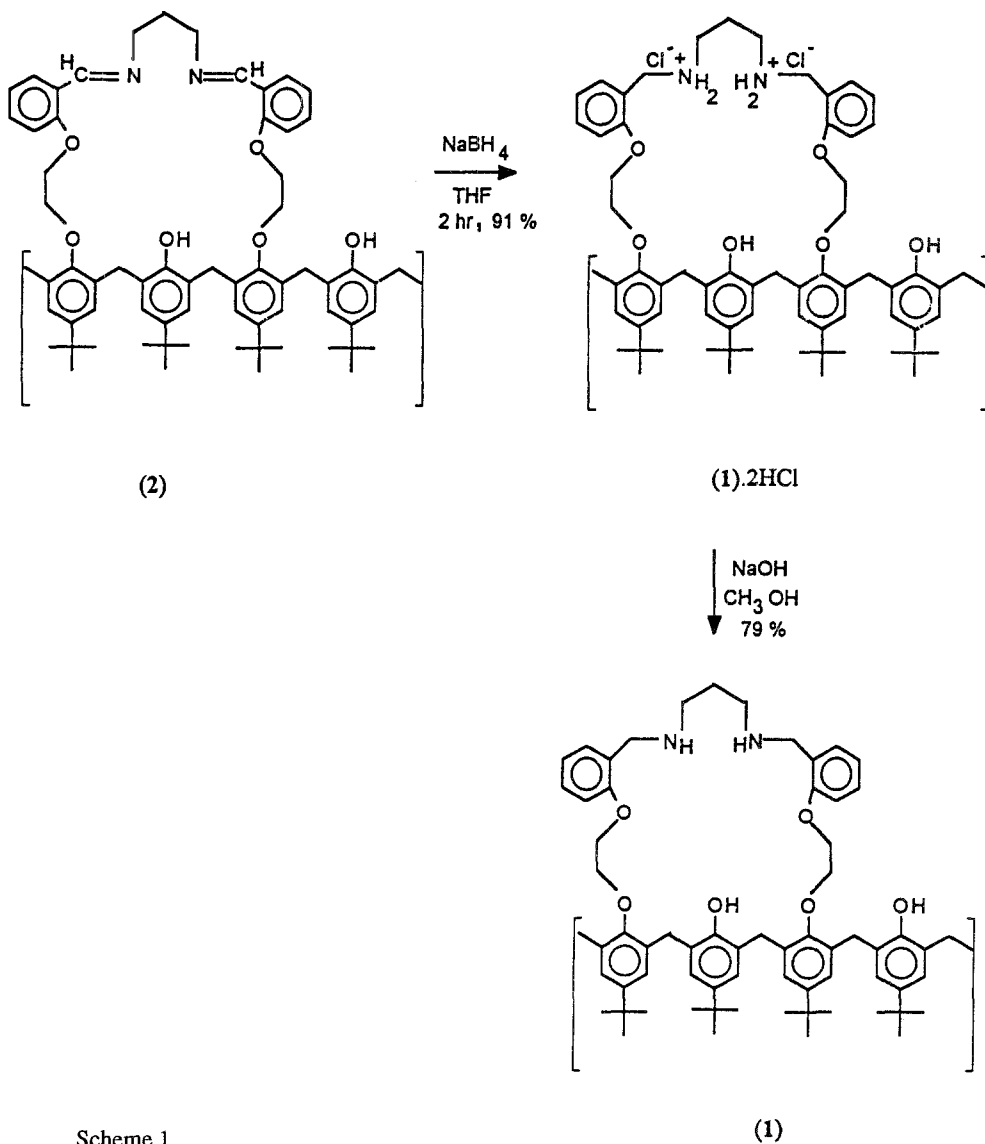
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The complexation ability of calix(aza-)crowns [6] and Schiff-base calix[4]arenes [8] towards soft cations, probably due to the presence of two nitrogen atoms in the bridge, led us to synthesize di-aza-benzo crown ether (**1**) derived from *p*-*tert*-butyl calix[4]arene. Receptors bearing diamino functions are known to coordinate zinc cation [9] and we also reported a preliminary complexation study for zinc(II) cation by (**1**).

2. Results and Discussion

The di-aza-benzo crown ether-*p*-*tert*-butyl calix[4]arene (**1**) was prepared by hydrogenating the Schiff-base calix[4]arene (**2**) (see Scheme 1 and [10]). In the first step, the Schiff-base calix[4]arene (**2**), prepared as described previously by us [8], was reacted with sodium borohydride (20 equiv.) in tetrahydrofuran with stirring under a nitrogen atmosphere for two hours. The hydrogenated product was obtained as a white solid in protonated form, (**1**).2HCl. The di-aza-benzo crown ether-*p*-*tert*-butyl calix[4]arene (**1**) could be obtained by neutralizing (**1**).2HCl with sodium hydroxide in methanol with 72% yield. The deprotonated form (**1**) seemed to be as stable as its protonated analogue. In ¹H-NMR spectra in CDCl₃ [10], the methylene protons Ar-CH₂-NH-, derived from the Schiff base imine Ar-CH=N- (**2**), shifted from 4.68 ppm in (**1**).2HCl to 3.86 ppm in (**1**). A similar upfield shift was also observed for the bridged propylene protons: NCH₂CH₂ at 3.70 and CH₂CH₂CH₂ at 2.90 ppm in (**1**).2HCl to 2.53 and 1.48 ppm, respectively. Compound (**1**) showed a cone conformation by giving two *p*-*tert*-butyl signals and one AB system for the methylene protons on the lower rim with a coupling constant of 13.2 Hz as also observed in the Schiff base analogue (**2**) [8].

The metal ion complexation of di-aza-benzo crown ether-*p*-*tert*-butyl calix[4]arene (**1**) with Zn²⁺ ion was studied by NMR spectroscopy. The 200 MHz ¹H-NMR spectrum of (**1**) recorded in a mixed CDCl₃/CD₃OD solvent is shown in Figure 1. Upon addition of Zn²⁺ [11], several downfield shifts were observed: the signals at 3.78 ppm (a) Ar-CH₂-N (3.86 ppm in CDCl₃) and 2.48 ppm (b) NCH₂CH₂ (2.53 ppm in CDCl₃) (see Figure 1) showed continuous downfield shifts, throughout the entire Zn²⁺: (**1**) mole ratios studied, which reached their maximum values after 26 days (Table I). Typical mole ratio plots for protons (a) and protons (e) are shown in Figures 2 and 3, respectively. Although larger shifts were observed for methylene protons (b), the values for the methylene protons (a) were chosen in the mole ratio plot (Figure 2) due to the overlapping of the solvent peaks with the methylene protons (b) at higher mole ratio values. The plot of data obtained immediately after mixing of the solutions (Figure 2) showed a well defined mole ratio plot for a 1 : 1 complex up to a mole ratio of 2 : 1. When the reaction solutions reached equilibrium, the plot (after 26 days) showed a 2 : 1 (Zn : (**1**)) complex formation by extrapolating the curve. We believe that the first Zn²⁺ located itself in the cavity near the nitrogen atoms of (**1**) since the shifting for the bridged propylene protons (b) next to the nitrogen atoms appeared to be the largest of all the shifts observed



Scheme 1.

(Table I). This first step formed a 1 : 1 complex and occurred instantaneously after mixing the reactant solutions. Therefore, a well defined mole ratio plot for 1 : 1 complex formation was obtained. The chemical shift displacement values between 1 and 3 equivalents increased significantly with time and metal concentration. This was interpreted as the formation of the 2 : 1 (Zn : (1)) species which showed slow kinetic behavior. Analysis of the data at equilibrium in Figure 2 showed the complex formation constants to be: $\log K_1 = 3.6$ and $\log K_2 = 3.0$. At the same time, we observed that while the signals for the *tert*-butyl (c) and aromatic protons

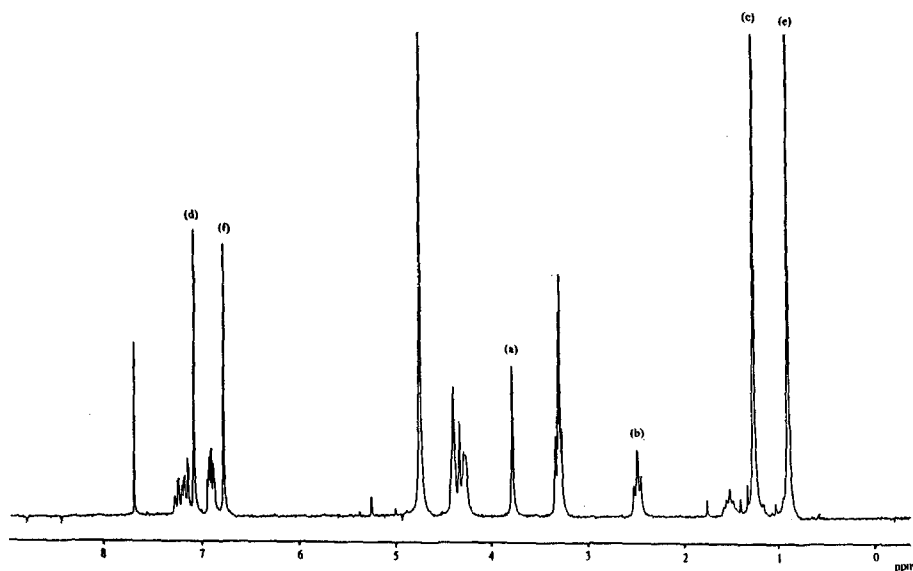


Fig. 1. $^1\text{H-NMR}$ spectrum ($\text{CDCl}_3+\text{CD}_3\text{OD}$) of (1).

(d) of the *p-tert-butyl-Ar-OH* units remained unchanged at 1.26 ppm (1.30 ppm in CDCl_3) and 7.10 ppm (7.04 ppm in CDCl_3), respectively the corresponding signals for the other half units, bearing the di-aza-crown coordinated to the first Zn^{2+} , at 0.91 ppm (e) (0.87 ppm in CDCl_3) and 6.77 ppm (f) (6.74 ppm in CDCl_3) showed first downfield shifts up to Zn^{2+} : (1) = 0.8 and then a reversal of direction until reaching the initial chemical shift values (Figure 3). The first downfield shift may correspond to the formation of the 1 : 1 complex in which the geometry of (1) has been changed by the coordination of the first Zn^{2+} with the nitrogen atoms of the di-aza unit leading to a new position for the *tert-butyl* groups. The reverse shifting may be due to the binding of the second Zn^{2+} during the formation of the 2 : 1 complex. The interaction between the second Zn^{2+} and the oxygen atoms on the lower rim may have brought the *p-tert-butyl* groups back, approximately, to their original position. A similar change in shift direction was also observed by Mei *et al.* [12] during the formation of a 2 : 1 complex from the 1 : 1 complex in the complexation process of 18-crown-6 with a Cs^+ ion.

In a separate experiment, the combined NMR solutions of mole ratios greater than 1 : 1 were evaporated to dryness and treated with diethyl ether to deposit a white solid proved to be of the 1 : 1 type by elemental analysis. Anal. Calcd. for $\text{C}_{65}\text{H}_{82}\text{O}_6\text{N}_2\text{Zn}(\text{ClO}_4)_2$: C, 62.37; H, 6.60. Found: C, 63.02; H, 6.95. The deposition of the solid 1 : 1 complex despite $^1\text{H-NMR}$ evidence for the formation of a 2 : 1 ($\text{Zn} : (1)$) complex was interpreted as an 'exclusive' [13] complexation of the second Zn^{2+} . A solid complex (3) prepared [14] separately by mixing

TABLE I. $^1\text{H-NMR}$ signal displacements, after 26 days, for protons (a), (b) and (e) of (1) upon adding $\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$.

Zn : (1)	Hz		
	(a)	(b)	(e)
0	0	0	0
0.2	9.9	21.2	5.9
0.4	18.2	38.3	11.0
0.6	30.5	64.5	18.6
0.8	41.8	86.5	22.2
1.0	61.2	112.1	15.1
1.2	69.1	122.7	12.1
1.5	74.9	129.6	9.9
2.0	85.3	143.0	5.4
2.5	98.2	–	0.9
3.0	104.2	–	0.0
4.0	104.3	–	0.0
5.0	104.4	–	0.0
6.0	104.3	–	0.0

– Non-readable values due to overlapping of the solvent signal.

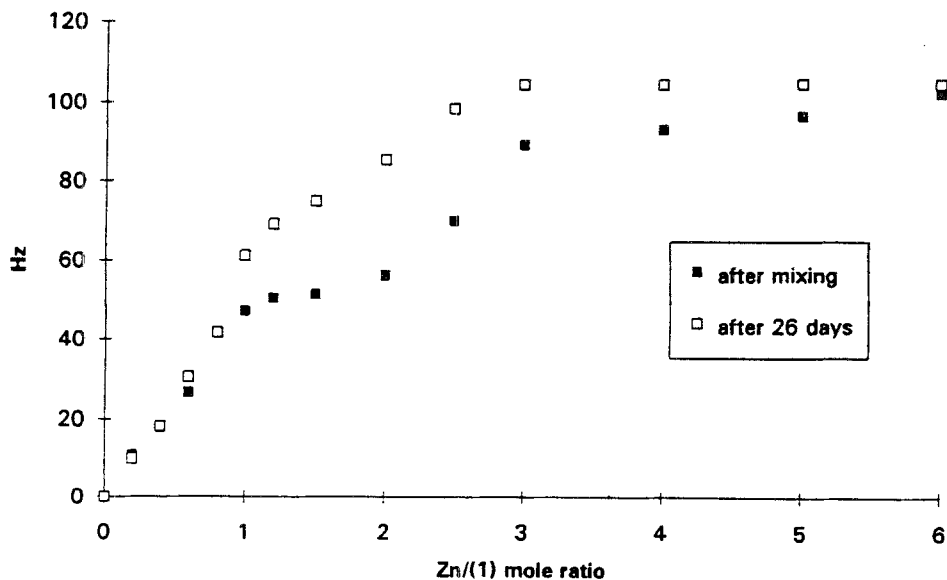


Fig. 2. Progressive chemical shift plot of protons (a) upon addition of Zn^{2+} up to 6 equivalents immediately after mixing and after 26 days.

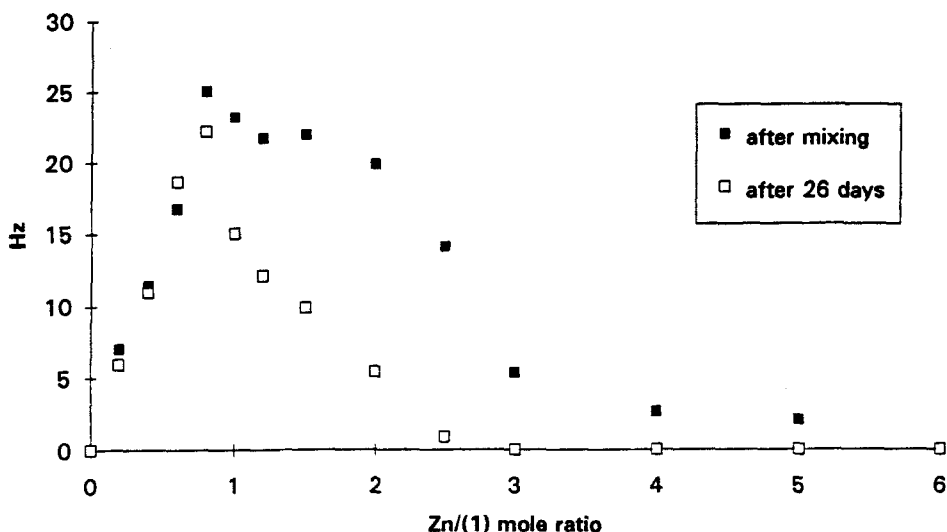


Fig. 3. Progressive chemical shift plot of protons (e) upon addition of Zn^{2+} up to 6 equivalents immediately after mixing and after 26 days.

$Zn(ClO_4)_2 \cdot 6H_2O$ and (1) with NaOH also yielded the same species as isolated from the NMR solutions.

3. Conclusion

To conclude, we report the synthesis of the new di-aza-benzo crown ether (1) derived from *p-tert*-butyl calix[4]arene. Ligand (1) was observed to complex zinc cation to form 1 : 1 and 2 : 1 (Zn : (1)) complexes. The 1 : 1 complex is relevant to zinc complexes related to zinc containing enzymes [15]. Work is proceeding in two directions: (i) to crystallize the 1 : 1 complex for its crystal structure determination and (ii) to complex organic anions by (1).2HCl.

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- A typical procedure is described for the preparation of (1): Schiff-base calix[4]arene (2) (10.00 g, 10.2 mmol) was stirred with sodium borohydride (7.84 g, 203.6 mmol) in tetrahydrofuran under a nitrogen atmosphere for two hours. After completion of the reaction, the unreacted sodium borohydride was quenched with water. After evaporating to dryness, the solid residue was then extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated to dryness. The solid was acidified with a hydrochloric acid solution in methanol (0.74% v/v) until the pH of the solution reached 1. The hydrogenated product was obtained as a white solid in protonated form, (1).2HCl. Yield: 9.86 g, 91%. Mp 277.1-277.6° C (dec.). The di-aza-benzo crown ether-*p-tert*-butylcalix[4]arene (1) was obtained by neutralizing (1).2HCl (2.00 g, 1.9 mmol) with NaOH (0.20 g, 5.0 mmol) in methanol (75 mL). A white precipitate was observed upon contact of the reactants. The solvent was evaporated to dryness under reduced pressure and the residue was extracted into dichloromethane. After drying over sodium sulfate, (1) was precipitated from the dichloromethane solution by adding methanol. Yield: 1.46 g, 79%. Mp 280.7-281.1° C (dec.).
Characterization data for (1).2HCl ¹H-NMR (CDCl₃): 9.66 (s, broad, 4H, NH), 7.40-7.30 and 6.95-6.90 (m, 8H, aromatic protons), 6.99 (s, 4H, HOArH), 6.82 (s, 2H, ArOH), 6.74 (s, 4H, ROArH), 4.68 (b, 4H, Ar-CH₂-NH-), 4.39 and 3.24 (AB system, J_{H-H} = 13.0 Hz, 8H, ArCH_AH_BAr), 4.23 (s, broad, 8H, OCH₂CH₂O), 3.70 (s, broad, 4H, NCH₂CH₂), 2.90 (s, broad, 2H, CH₂CH₂CH₂), 1.25 (s, 18H, HOAr-*t*-C₄H₉), 0.88 (s, 18H, ROAr-*t*-C₄H₉). FAB positive: 987.4. Anal. Calcd. for C₆₅H₈₂O₆N₂.2HCl.3CH₃OH(1156.42): C, 70.63; H, 8.37. Found: C, 70.78; H, 8.38.
For (1) ¹H-NMR (CDCl₃): 7.25-7.18 and 6.95-6.79 (m, 8H, aromatic protons), 7.04 (s, 4H, HOArH), 6.67 (s, 4H, ROArH), 6.36 (s, 2H, NH), 4.40 and 4.22 (broad, 8H, OCH₂O), 4.38 and 3.26 (AB system, J_{H-H} = 13.2 Hz, 8H, ArCH_AH_BAr), 3.86 (s, 4H, Ar-CH₂-NH-), 2.53 (t, J_{H-H} = 5.4 Hz, 4H, NCH₂CH₂), 1.48 (m, 2H, CH₂CH₂CH₂), 1.30 (s, 18H, HOAr-*t*-C₄H₉), 0.87 (s, 18H, ROAr-*t*-C₄H₉). FAB positive: 987.4. Anal. Calcd. for C₆₅H₈₂O₆N₂ (986.62): C, 79.07; H, 8.37. Found: C, 79.79; H, 8.42.
- The solutions for NMR complexation study were prepared by adding the methanol solution of Zn(ClO₄)₂.6H₂O into the chloroform solution of (1) so that the Zn²⁺: (1) mole ratio varied from 0 to 6. The concentration of (1) remained constant at 2.0 × 10⁻² M. The spectra were followed until no more shifts were observed after 26 days.
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- This procedure was adopted from [15]: (1) (0.17 g, 0.2 mmol) in chloroform was mixed with NaOH (16 mg, 0.4 mmol) and Zn(ClO₄)₂.6H₂O (0.29 g, 1.1 mmol) in methanol and the reaction mixture was stirred for two days. After evaporation to dryness, chloroform was added and the unreacted zinc salt was filtered off. The filtrate gave (3) upon standing for two days as yellowish-white needles.
Characterization data for (3) ¹H-NMR (CDCl₃): 7.43-7.34 and 7.02-6.94 (m, 8H, aromatic protons), 7.05 (s, 4H, HOArH), 6.63 (s, 4H, ROSrH), 6.18 (s, 2H, NH), 4.58 and 4.37 (broad, 8H, OCH₂CH₂O), 4.46 (s, 4H, Ar-CH₂-N), 4.23 and 3.29 (AB system, J_{H-H} = 13.4 Hz, 8H, ArCH_AH_BAr), 3.52 (broad, 4H, NCH₂CH₂), 2.70 (m, 2H, CH₂CH₂CH₂), 1.29 (s, 18H, HOAr-*t*-C₄H₉), 0.83 (s, 18H, ROAr-*t*-C₄H₉).

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